Part of #6

ATTORNEY'S DOCKET NO.: D0403/7019

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	F. Howard Schneider, Indu A. Muni, B. Ram Murty, Mahendra K. Pandya, and Rajinder P.S. Matharu
Serial No.:	08/145,203
Filed:	October 28, 1993
For:	METHODS AND ARTICLES OF MANUFACTURE FOR THE TREATMENT OF NICOTINE WITHDRAWAL AND AS AN AID IN SMOKING CESSATION
Examiner:	S. Rose
Art Unit:	1205

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

The undersigned hereby certifies that this document is being placed in the United States mail with first-class postage attached, addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the 29th of August, 1994.

Anthony J. Janiuk, Reg. No. 29,809

HON. COMMISSIONER OF PATENTS
AND TRADEMARKS
WASHINGTON, D.C. 20231

AFFIDAVIT UNDER RULE 132

Dear Sir:

Commonwealth of Massachusetts)
) s.s.
County of Suffolk)

F. Howard Schneider, being duly sworn, deposes and says:

1. I am a co-inventor of the subject matter of the above-identified application.

2. I have received a Bachelor of Science and a Master of Science degree in chemistry from Arizona State University. I have received a Doctor of Philosophy degree in pharmacology from Yale University School of Medicine.

3. I am employed by the assignee of the present application in the position of Senior Vice President, Technology.

4. I am skilled in the art of pharmaceutics and have been involved with smoking cessation studies since 1990.

5. I have experience in collecting and interpreting clinical data and am qualified to interpret the data presented in this Affidavit.

6. The data presented in this Affidavit is clinical data for submission to the FDA. Assignee of the present invention intends to submit a NDA for prescription drug status for the article of manufacture and method of the present invention.

7. Upon information and belief, sublingual tablets were prepared and evaluated clinically. These sublingual tablets comprised 2.5 mg L-lobeline sulfate, 5.0 mg L-lobeline sulfate, 7.5 mg L-lobeline sulfate or an inert material to form placebo sublingual tablets. These tablets were administered to

22 subjects who regularly smoked nicotine cigarettes. The strength and number of tablets administered per day determined the total daily dose. The amount of lobeline sulfate administered sublingually per day was plotted against the Tobacco Withdrawal Syndrome Index (TWSI) score averaged for each subject. The TWSI is a system for evaluating symptoms of tobacco smoking withdrawal on a 0-4 scale. The components of TWSI which were evaluated comprised anxiety, anger, craving for a cigarette, restlessness and difficulty concentrating. The TWSI scores were obtained in three separate 42-44 hour sessions, one in each of three consecutive weeks. The subjects spent two nights in the clinic and abstained from smoking over the full time. Subjects entered the clinic at noon on Day 1 and immediately ceased tobacco consumption. At 7:00 a.m. the next morning they started taking either placebo or l-lobeline sulface sublingual tablets, which they continued to take periodically over the next 16 hours, the total amount taken being dependent on the dose group to which they belonged and the strength of tablet. TWSI scores were taken periodically throughout the day. The results are depicted in Figure 1 of this Affidavit. In Figure 1, "P" is used to indicate the use of placebo sublingual tablets containing no lobeline. The line marked with "2" indicates the response to the use of 2.5 mg L-lobeline sulfate sublingual tablets. The line marked "5" indicates the response to 5.0 mg L-lobeline sulfate sublingual tablets. And, the line marked "7" indicates the response to

7.5 mg L-lobeline sulfate sublingual tablets. These results suggest a marked reduction in nicotine withdrawal symptoms with increasing doses of L-lobeline sulfate. These results suggest that an effective amount is approximately 30-90 mg L-lobeline sulfate administered sublingually per day.

8. Upon information and belief, these results suggest that L-lobeline sulfate sublingual tablets are effective and have utility to alleviate nicotine withdrawal symptoms.

This statement is made with the knowledge that knowingly and willfully false, fictitious or fraudulent statements or representations, or the making or using any false writing or document, knowing the same to contain any false, fictitious or fraudulent statement or entry may subject me to imprisonment or fines or both.

Further affiant sayeth not.

F. Howard Schneider

State of Massachusetts
County of Suffolk

Subscribed and sworn before me this 29th day of August, 1994.

SEAL

Notary Public
No. 83165

ATTORNEY'S DOCKET NO.: D0403/7019

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	F. Howard Schneider, Indu A. Muni, B. Ram Murty, Mahendra K. Pandya, and Rajinder P.S. Matharu
Serial No.:	08/145,203
Filed:	October 28, 1993
For:	METHODS AND ARTICLES OF MANUFACTURE FOR THE TREATMENT OF NICOTINE WITHDRAWAL AND AS AN AID IN SMOKING CESSATION
Examiner:	S. Rose
Art Unit:	1205

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

The undersigned hereby certifies that this document is being placed in the United States mail with first-class postage attached, addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the 29th of August, 1994.

Anthony J. Janiuk, Reg. No. 29,809

HON. COMMISSIONER OF PATENTS
AND TRADEMARKS
WASHINGTON, D.C. 20231

Sir:

TRANSMITTAL LETTER

Transmitted herewith for filing is/are the following document(s):

[X] Response and Submission of Affidavit Under 37 C.F.R. 1.132
[X] Affidavit under Rule 132 (fax copy)
[X] Petition for One Month Extension of Time

If the enclosed papers are considered incomplete, the Mail Room and/or the Application Branch is respectfully requested to contact the undersigned collect at (617)720-3500, Boston, Massachusetts.

A check in the amount of $55.00 is enclosed to cover the extension fee. If the fee is insufficient, the balance may be charged to the account of the undersigned, Deposit Account No. 23/2825. A duplicate of this sheet is enclosed.

Respectfully submitted,

Anthony J. Janiuk, Reg.No.: 29,809
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210
TEL.: (617) 720-3500

ATTORNEY'S DOCKET NO.: D0403/7019
DATE: August 29, 1994

PATENT SPECIFICATION

DRAWINGS ATTACHED

Inventor: SIDNEY SAMUEL HART

1,017,032

1,017,032

Date of filing Complete Specification Dec. 8, 1964.

Application Date Dec. 12, 1963. No. 49162/63.

Complete Specification Published Jan. 12, 1966.

Index at acceptance: —C4 X11; A5 B(1R1, 7); F1 R3A3D

Int. Cl.:—**A 61m 11/00//A 61 k, F 05 d**

COMPLETE SPECIFICATION

Aerosol Compositions

We, AEROSMOKE LIMITED, a British Company, of Cheriton, Pyle Hill, Newbury, Berkshire, (formerly of Kings Road Trading Estate, Newbury, Berkshire), do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to appliances for reducing the tendency to smoke tobacco.

In accordance with the present invention there is provided an appliance for reducing the tendency to smoke tobacco which comprises an aerosol dispenser of the type which delivers a fixed amount of aerosol composition at each operation and which contains, as an anti-smoking composition, an alkaloid of the kind which acts as a substitute for nicotine by at least partly satisfying the craving therefor uniformly dispersed in an aerosol propellant vehicle, the said fixed amount and the concentration of the alkaloid in the composition being such that from 0.05 to 0.3 mg. of the alkaloid, reckoned as lobeline hydrochloride on an efficacy basis, is delivered at each operation of the dispenser. The preferred alkaloid is lobeline itself. It is advantageously present in the form of the hydrochloride which has better solubility properties than other simple salts, notably lobeline sulphate.

It is well known to provide anti-smoking tablets containing lobeline, to act as a substitute for nicotine as aforesaid, in the form of lobeline sulphate. They commonly contain about 2 mg. of lobeline sulphate and are taken one three times per day to supply the user with about 6 mg. of lobeline sulphate daily. With the present appliance the user inhales the alkaloid-containing fine droplets produced on operating the dispenser and it is found that the alkaloid is very much more effective, weight for weight, in this form than in the form of tablets. For example, with an appliance arranged to deliver about 0.1 mg. of lobeline hydrochloride per operation which is the preferred delivery, the inhalation of the droplets from ten operations per day, containing in all about 1 mg. of lobeline hydrochloride, has substantially the same effect as the three tablets containing a total of 6 mg. of lobeline sulphate, that is to say it will satisfy the craving for nicotine of most moderate smokers. Because of the very high cost of lobeline the saving in cost is considerable.

The appliance may be provided to give amounts other than 0.1 mg. in the range from 0.05 to 0.3 mg. at each operation if desired. Larger amounts in the range are useful in cases where 0.1 mg. proves to be insufficient for the user and smaller amounts are useful for users who prefer a shorter interval than one hour between inhalations. Especially in the latter connection, it is to be noted that use of the appliance, like taking and lighting a cigarette requires manipulation and in very many cases the provision of something to manipulate is advantageous in itself. Indeed the present invention makes it practicable for a smoker to employ a lobeline composition regularly at little cost, e.g. as frequently as he would otherwise have recourse to a cigarette. He may choose between using the composition to reduce the number of cigarettes consumed and using it in conjunction with an endeavour to dispense with cigarettes entirely.

When lobeline is provided in the form of tablets, it is necessary to incorporate antacids in order to prevent nausea. No such additive is required with the present inhalant composition.

It is preferred that lobeline, when employed, should be present in the composition in a concentration, reckoned as the hydrochloride,

of from 0.2 to 0.3% by weight. Similarly, alkaloids other than lobeline are preferably present in an equivalent concentration reckoned on an efficacy basis; thus an alkaloid which is twice as effective, weight for weight, as lobeline is preferably present in a concentration of from 0.1 to 0.15% by weight. At such a concentration, the user obtains the lobeline or other alkaloid in an effective amount by dispensing and inhaling a convenient amount of the composition; moreover, aerosol dispensers of the fixed dosage type which deliver the appropriate amount of the composition are readily obtainable in the trade.

The following typical examples are given in order to illustrate the invention.

EXAMPLE I

A composition was prepared from

0.25% by weight of lobeline hydrochloride.
25.0% by weight of ethanol, and
74.75% by weight of symmetrical dichlortetrafluoro-ethane, as aerosol propellant vehicle.

100%

The amount of the composition providing 0.1 mg. of lobeline hydrochloride was 0.040 gram. Accordingly, an aerosol dispenser small enough to be carried conveniently in the pocket contained sufficient lobeline hydrochloride for 200 inhalations.

Lobeline hydrochloride was employed rather than the sulphate because of its greater solubility. Especially if an amount of the hydrochloride greater than 0.25% by weight is to be provided, part of the alcohol is advantageously replaced by chloroform, propylene glycol or other co-solvent in order to minimise the danger of partial precipitation of the hydrochloride on storage.

EXAMPLE 2

A composition was prepared from

0.25% by weight of lobeline hydrochloride
0.25% by weight of ascorbic acid
5.00% by weight of propylene glycol
19.50% by weight of ethanol
75.00% by weight of symmetrical dichlorotetrafluoro-ethane as aerosol propellant vehicle.

The ascorbic acid was provided as an antioxidant. In the absence thereof the composition becomes discoloured on standing for prolonged periods, the tendency being substantially less however when chloroform is the co-solvent.

Best results are obtained with the foregoing compositions using a fixed dosage aerosol dispenser provided with a tube along which spray from the spray nozzle of the dispenser may be directed towards the mouth of the user, a wide telescopic tube being preferred. From the tube the dispensed composition emerges with the appearance of a puff of smoke. The particle size of the composition appears to depend upon the extension of the tube. The mechanics of the tube are not fully understood, but it appears that the stationary mass of air present in the tube reacts mechanically upon the jet of droplets produced by the nozzle, not only to slow them, but also to break them up to form a smoke-like cloud of very fine particles, the vast majority of which are about 5 microns in diameter for a full extension of the tube. Such a cloud, is quite different in its appearance from the original jet of droplets which typically has a particle size of from 25 to 30 microns. On inhalation the particles are, because of their very fine size, able to pass to the alveoli in somewhat the same manner as tobacco smoke and from there, have their active component absorbed into the blood stream. They are not however so small that they fail to deposit and become ejected at the next breath.

A suitable dispensing apparatus having a telescopic tube is shown by way of example in the accompanying drawing, in which:

Figure 1 is a part sectional side elevation of the apparatus, and

Figure 2 shows a part of the apparatus in perspective.

In the said dispensing apparatus a conventional glass aerosol bottle 1 has a projecting tube 2 over which is fitted a conventional button 3 incorporating a spray nozzle having an outlet at 4. Pressing the tube 2 downwardly by the button 3 causes a metered quantity, e.g. 0.040 gram. of aerosol composition 5, containing 0.1 mg. of lobeline hydrochloride to be delivered as a jet of droplets from outlet 4.

Force fitted over the button 3 is a telescopic tube 6 having an outlet diameter at end 7 of 2.2 cm. The length of the tube from end 7 to the nozzle is variable from 7.1 cm. to 12.5 cm. The end of the telescopic tube behind the nozzle has an integral end closure 8 covered by a cap 9 rotatably secured thereto by a necked protuberance 10 sprung through an aperture in said end closure. Cap 9 is formed with air openings 11 which register with corresponding openings in the end closure 8 when openings in the telescopic tube 6 and cap 9 are registered together to admit the tube 2.

To use the dispenser, the user places the end 7 between his lips and inhales whilst pressing upon a ribbed flat surface 12 provided on the cap. The pressure causes the tube 6, the button 3 and the tube 2 to move downwardly together. In the result the jet of droplets from outlet 4 reacts mechanically with the air in the tube 6 to provide a smoke-like cloud for inhalation by the user.

The telescopic tube 6 and the button 3 together form an assembly which can be lifted off the tube 2. The size of the bottle 1 is such that it may be inserted into the tube

through end 7 to provide a compact package, suitable for carriage in the user's pocket, in which package the tube 2 is protected. This size of bottle contains sufficient composition for about 200 inhalations, i.e. for nearly three weeks at ten inhalations per day.

Besides providing the user with an inhalation of an alkaloid as would smoking tobacco, the dispenser also provides him with something to manipulate. In view of the manipulations involved in smoking a cigarette, this factor is probably important psychologically.

As will be appreciated by those skilled in the art, various departures may be made from the compositions shown in the foregoing typical examples without departing from the ambit of the invention. For example aerosol propellants other than symmetrical dichlorotetrafluoro-ethane may be employed especially other chlorinated or chlorofluorinated methanes and ethanes having suitable boiling points, well known examples thereof being dichlorodifluoromethane, dichloromonofluoro-methane, monochlorotrifluoromethane as well as mixtures of these propellants with one another and/or with dichlorotetrafluoromethane. Similarly solvents other than ethanol and co-solvents other than chloroform or propylene glycol may also be employed to ensure that the solubility of the alkaloid in the mixture is sufficient to maintain stability on storage. Anti-oxidants of the kind used in food preparations, other than ascorbic acid, may be employed where desired, although ascorbic acid is preferred, being a substance which can be expected to yield no unwanted effects when inhaled. Typical of other anti-oxidants are sodium bisulphite, the tocopherols, *d*-glucoascorbic acid, *d*-isoascorbic acid, sodium formaldehyde sulphoxylate and sodium thioglycolate.

If desired, part of the lobeline or other alkaloid may be replaced by an equivalent amount of nicotine and/or olfactory material; for example socratine which is responsible, at least in part,for the odour of tobacco, may be incorporated in the composition.

WHAT WE CLAIM IS:—

1. An appliance for reducing the tendency to smoke tobacco which comprises an aerosol dispenser of the type which delivers a fixed amount of aerosol composition at each operation and which contains, as an anti-smoking composition, an alkaloid of the kind which acts as a substitute for nicotine by, at least partly, satisfying the craving therefor uniformly dispersed in an aerosol propellant vehicle, the said fixed amount and the concentration of the alkaloid in the composition being such that from 0.05 to 0.3 mg. of the alkaloid, reckoned as lobeline hydrochloride on an efficacy basis, is delivered at each operation of the dispenser.

2. An appliance according to Claim 1 in which the alkaloid is present in a concentration of from 0.2 to 0.3% by weight reckoned as lobeline hydrochloride on an efficacy basis.

3. An appliance according to either of Claims 1 or 2 in which the alkaloid is lobeline.

4. An appliance according to either of Claims 1 or 2 in which the alkaloid is lobeline present as lobeline hydrochloride.

5. An appliance according to Claim 4 in which the said fixed amount and the concentration are such that about 0.1 mg. of lobeline hydrochloride is delivered at each operation of the dispenser.

6. An appliance according to either of Claims 4 or 5 in which the aerosol propellant vehicle contains ethanol and chloroform as co-solvents for the lobeline hydrochloride.

7. An appliance according to either of Claims 4 or 5 in which the aerosol propellant vehicle contains ethanol and propylene glycol as co-solvents for the lobeline hydrochloride.

8. An appliance according to any one of Claims 1 to 7 in which the composition contains an anti-oxidant.

9. An appliance according to Claim 8 in which the anti-oxidant is ascorbic acid.

10. An appliance according to any one of Claims 1 to 9 provided with a tube along which spray from the spray nozzle of the dispenser may be directed towards the mouth of the user.

11. An appliance according to Claim 10 in which the tube is removable from the dispenser and is dimensioned to house the dispenser after removal therefrom.

12. An appliance according to either of Claims 10 or 11 in which the tube is a telescopic tube.

13. An appliance for reducing the tendency to smoke tobacco substantially as hereinbefore described and illustrated by the foregoing Examples and accompanying drawing.

ALAN TROMANS & CO.,
Chartered Patent Agents,
Chancery House,
Chancery Lane,
London, W.C.2., England.

Leamington Spa: Printed for Her Majesty's Stationery Office by the Courier Press.—1966.
Published at The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

1017032 COMPLETE SPECIFICATION
1 SHEET *This drawing is a reproduction of the Original on a reduced scale*

Fig. 1.

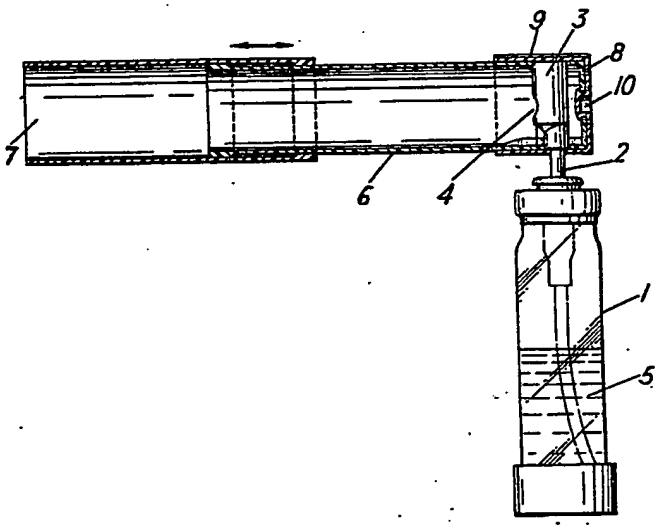
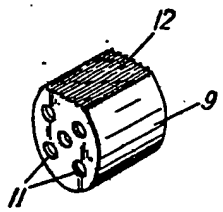


Fig. 2.



ATTORNEY'S DOCKET NO.: D0403/7019

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: F. Howard Schneider, Indu A. Muni, B. Ram Murty, Mahendra K. Pandya, and Rajinder P.S. Matharu
Serial No.: 08/145,203
Filed: October 28, 1993
For: METHODS AND ARTICLES OF MANUFACTURE FOR THE TREATMENT OF NICOTINE WITHDRAWAL AND AS AN AID IN SMOKING CESSATION

Examiner: S. Rose
Art Unit: 1205

CERTIFICATE OF MAILING UNDER 37 C.F.R. §1.8(a)

The undersigned hereby certifies that this document is being placed in the United States mail with first-class postage attached, addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the 1st of November, 1994.

Anthony J. Janiuk, Reg. No. 29,809

HON. COMMISSIONER OF PATENTS
AND TRADEMARKS
WASHINGTON, D.C. 20231

SECOND AFFIDAVIT UNDER RULE 132

Dear Sir:

Commonwealth of Massachusetts)
) s.s.
County of Suffolk)

F. Howard Schneider, being duly sworn, deposes and says:

1. I am a co-inventor of the subject matter of the above-identified application.

2. I have received a Bachelor of Science and a Master of Science degree in chemistry from Arizona State University. I have received a Doctor of Philosophy degree in pharmacology from Yale University School of Medicine.

3. I am employed by the assignee of the present application in the position of Senior Vice President, Technology.

4. I am skilled in the art of pharmaceutics and have been involved with smoking cessation studies since 1990.

5. I have experience in collecting and interpreting clinical data and am qualified to interpret the data presented in this Affidavit.

6. The data presented in an Affidavit filed August 29, 1994 and the data presented in this Affidavit is clinical data for submission to the Food and Drug Administration (FDA). Assignee of the present invention intends to submit a New Drug Application (NDA) for prescription drug status for the article of manufacture and method of the present invention. The clinical data is being generated under an Investigational New

Drug Application (IND). Assignee of the present application for patent is the sponsor of the study. An IND number 44,066 has been assigned by the FDA for this study. A copy of Ms. Sharon Schmidt's letter to Peter J. Mione in which an IND number was assigned is attached hereto as Exhibit A.

7. On information and belief, a clinical study was initiated under the IND by the assignee through Leecoast Research Center, Inc. A true copy of the Clinical Study Protocol is attached hereto as Exhibit B. This study protocol is essentially the same as that upon which clinical trials of nicotine gum and nicotine transdermal patches were conducted and subsequently approved by the FDA. A summary of the protocol is set forth in paragraph 8 of this Affidavit.

8. On information and belief, approximately 156 smokers were enrolled in the study. These smokers were randomly divided into four groups. One group received 30 mg l-lobeline sulfate/per day administered as 5 mg l-lobeline sulfate sublingual tablets 6 times per day. A second group received 45 mg l-lobeline sulfate/per day administered as 5 mg l-lobeline sulfate sublingual tablets nine times a day. A third group received 67.5 mg l-lobeline sulfate/per day

administered as 7.5 mg l-lobeline sulfate sublingual tablets 9 times per day. A fourth group received a placebo administered nine times per day. Each individual of each group received brief (5 to 10 minutes) once a week behavioral counseling. Lobeline tablets were made in accordance with the present invention. The lobeline tablets were formulated to mask the taste of lobeline. The placebo tablets were formulated to imitate the flavor of lobeline tablets.

9. Upon information and belief, the results of the study suggest that lobeline, administered sublingually, in rapid disintegrating tablets, can be administered safely with no clinically significant adverse effects.

10. Upon information and belief, the results of the study suggest that lobeline, administered sublingually, in rapid disintegrating tablets is effective to alleviate tobacco withdrawal symptoms and reduce the number of cigarettes smoked per day.

11. Upon information and belief, results of the study with respect to smoking activity are summarized in Table 1 below:

Table 1

NicErase™-SL PHASE 2b: SMOKING ACTIVITY

Group	Cigarettes Smoked Per Week	
	pre-Study	Study Weeks 3-6
All Subjects Minus Dropouts		
Placbo (n=29)	214	45
Low (n=17)	215	38
Medium (n=22)	199	69
High (n=18)	203	34
≥ 77% Compliant to Therapy		
Placebo (n=19)	223	39
Low (n=6)	224	41
Medium (n=13)	198	49
High (n=9)	215	13
100% Compliant to Therapy		
Placebo (n=9)	233	60
Low (n=5)	244	48
Medium (n=5)	228	63
High (n=2)	257	1

Consistent with FDA guidelines, treatment efficacy was evaluated during weeks 3-6 of the study. The results of the low and medium doses of lobeline are not as clear as the high

dose due to the small enrollment number of this study. The low and medium doses may also be less than optimal for a percentage of the population. The low and medium dose results are, therefore, more variable. However, these results do suggest that lobeline administered sublingually is more effective than a placebo. The results suggesting a reduction of cigarettes smoked, from well over 200, down to one to 13, with respect high doses of lobeline, is striking.

12. Upon information and belief, results of the study with respect to abstinence rates are summarized in Table 2 below:

Table 2

NicErase™-SL PHASE 2b: ABSTINENCE RATES

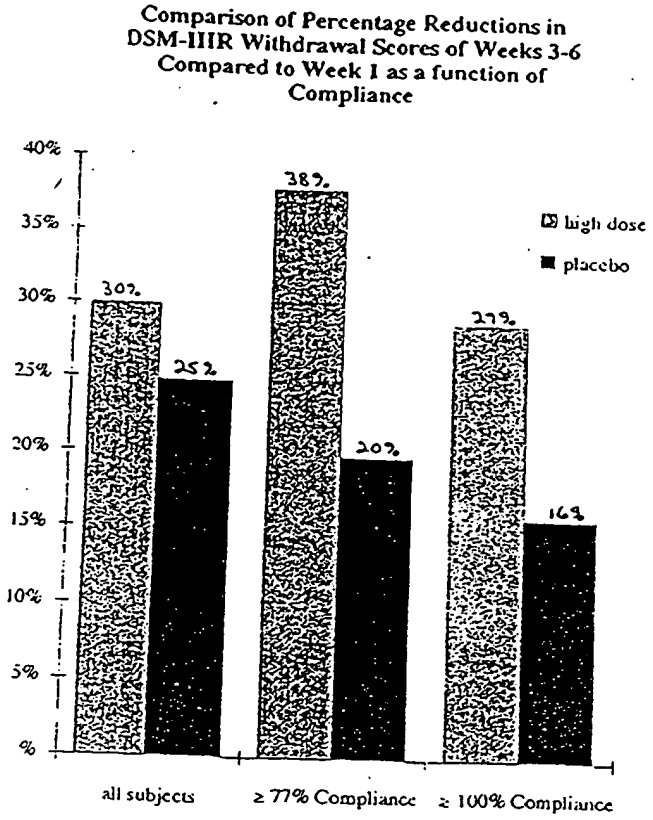
Group	n	Successes	Failures	Dropouts	Efficacy for All Subjects %	Efficacy for All, Minus Dropouts %
All Subjects						
Placebo	38	8	28	2	21	22
Low	39	7	18	14	18	28
Medium	39	7	22	10	18	24
High	38	6	17	15	16	26
≥ 77% Compliant to Therapy						
Placebo	24	5	19			21
Low	10	4	6			40
Medium	18	4	14			22
High	14	5	9			36
100% Compliant to Therapy						
Placebo	14	4	10			29
High	7	2	5			29
Medium	8	2	6			25
High	3	1	2			33

Smoking activity, expressed either as the number of cigarettes smoked or as total abstinence from smoking, was clearly reduced for those subjects who complied with therapy to an extent of taking at least 77% of their recommended doses. With respect to Table 2, within those individuals who were identified as 100% compliant, there is one individual who received high dose lobeline and who smoked one cigar and as a result is identified as a failure. This individual apparently did not understand that he was not allowed to smoke a cigar and still be considered abstinent from smoking. However, had this individual not smoked that one cigar, the efficacy of high dose lobeline would be even higher at 66%. The results of the low and medium doses of lobeline are not as clear as the high dose due to the small enrollment number of this study. The low and medium doses may also be less than optimal for a percentage of the population. The low and medium dose results are, therefore, more variable. These results are striking in demonstrating a high level of efficacy in promoting abstinence.

13. Upon information and belief, the results with respect to smoking withdrawal scores, for the high dose lobeline group compares to placebo is set forth in Figure 1 below:

Figure 1

DSM-IIIR Withdrawal Average Scores for 9x7.5mg and 9x0mg Treatment Groups



The difference between the placebo and the lobeline group became greater as compliance to therapy increased, again indicating that lobeline reduces tobacco withdrawal symptoms. The results of Figure 1 are striking in demonstrating a reduction in smoking withdrawal symptoms.

14. Upon information and belief, these results have been accepted by the FDA to allow the assignee of the present invention to conduct Phase 3 human clinical studies.

15. Upon information and belief, these results suggest that L-lobeline sulfate sublingual tablets are effective and have utility to alleviate nicotine withdrawal symptoms.

This statement is made with the knowledge that knowingly and willfully false, fictitious or fraudulent statements or representations, or the making or using any false writing or document, knowing the same to contain any false, fictitious or fraudulent statement or entry may subject me to imprisonment or fines or both.

Further affiant sayeth not.

F. Howard Schneider

State of Massachusetts
County of Suffolk

Subscribed and sworn before me this 28TH day of OCTOBER, 1994.

Notary Public

SEAL

4224R

DEPARTMENT OF . ıLTH & HUMAN SERVICES

EXHIBIT A

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 44,066

DEC 8 1993

DynaGen, Inc.
99 Erie Street
Cambridge, MA 02139

Attention: Peter J. Mione
Vice President, Clinical and Regulatory Affairs
Dear Mr. Mione:

We are pleased to acknowledge receipt of your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 44,066

Sponsor: DynaGen, Inc.

Name of Drug: NicErase™-SL (lobeline sulfate) sublingual

Date of Submission: Nov. 29, 1993

Date of Receipt: Nov. 30, 1993

IT IS UNDERSTOOD THAT STUDIES IN HUMANS WILL NOT BE INITIATED UNTIL 30 DAYS AFTER THE DATE OF RECEIPT SHOWN ABOVE. If, within the 30 day period, we notify you of serious deficiencies that require correction before human studies can begin or that would require restriction of human studies until corrected, it is understood that you will continue to withhold or restrict such studies until you are notified that the material you have submitted to correct the deficiencies is considered satisfactory.

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations promulgated thereunder. Those responsibilities include reporting any unexpected fatal or life-threatening experiences by telephone to this Agency no later than three working days after receipt of the information (21 CFR 312.32) and the submission of annual progress reports.

Please forward all future communications concerning this IND in TRIPLICATE identified with this IND number and addressed as follows:

Pilot Drug Evaluation Staff, HFD-007
Attention: DOCUMENT CONTROL ROOM # 9B-23
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours,

Sharon D. Schmidt

Project Manager
Pilot Drug Evaluation Staff
Center for Drug Evaluation and Research
(301) 443-3741